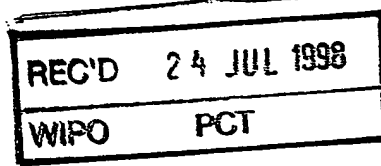




**Patent  
Office**

**09/445375**

The Patent Office  
Concept House  
Cardiff Road  
Newport  
South Wales  
NP9 1RH



I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed *Andrew Gersey*  
Dated 7th July 1998

**PRIORITY  
DOCUMENT**

SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17.1(a) OR (b)

# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road  
Newport  
Gwent NP9 1RH

1. Your reference

KP/2594

4 JUN 1997

2. Patent application number

(The Patent Office will fill in this part)

9711579.4

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Oxford BioMedica (UK) Limited  
Medawar Centre  
Robert Robinson Avenue  
The Oxford Science Park  
Oxford  
OX4 4GA

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

THERAPEUTIC GENES

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

STEVENS, HEWLETT & PERKINS  
1 Serjeants' Inn  
Fleet Street  
London  
EC4Y 1LL

D. Young & Co.  
21, New Fetter Lane  
LONDON  
EC4A 1DA

Patents ADP number (if you know it)

1545003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number  
(if you know it)

Date of filing  
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

independent replication to produce infectious retroviral particles. Usually, a recombinant retroviral vector lacks functional *gag-pol* and/or *env* genes, or other genes encoding proteins essential for replication. A "targeted retroviral vector" is a recombinant retroviral vector whose ability to infect a cell or to be expressed in the target cell is restricted to certain cell types within the host organism. An example of targeted retroviral vectors is one with a genetically modified envelope protein which binds to cell surface molecules found only on a limited number of cell types in the host organism. Another example of a targeted retroviral vector is one which contains promoter and/or enhancer elements which permit expression of one or more retroviral transcripts in only a proportion of the cell types of the host organism.

An "envelope" protein is a viral protein which coats the viral particle and plays an essential role in permitting viral entry into a target cell.

"Transduction" is the process of using a viral vector to deliver a non-viral gene to a target cell. "Transfection" is a process using a non-viral vector to deliver a gene to a target mammalian cell.

"Immunoglobulin" is the term given to a member of a family of related multimeric proteins which are normally secreted from cells of the B-lymphocyte lineage of a vertebrate, whose function is to bind specifically with a region of a macromolecule identified as non-self. Immunoglobulins represent a major component of the immune response repertoire of the organism and are synonymous with "antibodies".

In its primary aspect the invention relates to the delivery of TBP-encoding genes to the site of a tumour. This has considerable advantages for therapeutic applications in which TBPs are indicated since it circumvents a number of problems associated with delivery of proteins systemically in man. Proteins are complex molecules which, of necessity, are produced from biological sources, most usually from genetically engineered organisms or cell cultures. The procedures for production of

TBPs are consequently complicated, labour intensive and costly.

Furthermore, pharmacological properties and other aspects of the function of TBPs such as immunoglobulins derived from non-human biological sources may frequently differ in important ways from the activity of the

5 corresponding natural human immunoglobulins produced in human cells.

One major cause of such differences in activity is variations in the pattern of glycosylation of proteins derived from different species (reviewed in Bebbington 1995; In Monoclonal Antibodies: the second generation ed . H. Zola pg 165-181). Systemic administration of TBPs containing toxin

10 domains can identify additional pharmacokinetic and toxicological problems (reviewed in Scheinberg and Chapman 1995. In Monoclonal antibodies (ed. Birch and Lennox) Chapter 2.1).

In contrast to the problems associated with production and delivery of proteins, the methods of the invention allow the delivery of  
15 genes to the site of the tumour, thus circumventing a number of production problems. The TBPs are thereby produced *in situ* in the autologous human cells, which serve as a local factory for the production of the gene-based therapeutic. This has significant advantages in minimising systemic toxicity. The activity of the protein is maximal since the glycosylation of the  
20 protein shows a human pattern appropriate to the individual being treated.

The methods of the invention can be used in conjunction with direct injection into the site of the tumour or systemic delivery of, for example targeted vectors or engineered myeloid cells or their progenitors. Systemic delivery may be particularly advantageous in a number of  
25 indications, particularly in the treatment of disseminated disease. In these cases the gene delivery system or engineered cells can be administered intravenously by bolus injection or by infusion in a suitable formulation. A pharmaceutically acceptable formulation may include an isotonic saline solution, a buffered saline solution or a tissue-culture medium. Additional

formulatory agents may be included such as preservative or stabilising agents.

The invention will now be further described by way of examples, which are meant to serve to assist one of ordinary skill in the art in carrying out the invention and are not intended in any way to limit the scope of the invention.

10

## EXAMPLES

15

### **Example 1 – Construction of 5T4 Sab and retroviral - vector delivery to tumour.**

The trophoblast cell surface antigen, originally defined by monoclonal antibody 5T4 (Hole and Stern 1988 Br. J. Cancer 57; 239-246), is expressed at high levels on the cells of a wide variety of human carcinomas (Myers et al. 1994 J. Biol. Chem. 269; 9319-9324) but, in normal tissues of non-pregnant individuals, is essentially restricted to low level expression on a few specialised epithelia (Myers et al. *ibid.* and references therein). The 5T4 antigen has been implicated in contributing to the development of metastatic potential and therefore antibodies specifically recognising this molecule may have clinical relevance in the treatment of tumours expressing the antigen.

The cDNA encoding the murine 5T4 monoclonal antibody is cloned and sequenced by standard techniques (Antibody engineering: a practical approach ed McCafferty et al. 1996 OUP). The sequence of the

30

variable region of the antibody can be used to construct a variety of immunoglobulin-like molecules including scFvs. The coding sequence of a 5T4 scFv, 5T4scFv.1, is shown in Figure 1. In this molecule, the DNA sequence encodes the Vh from the mouse 5T4 monoclonal antibody followed by a 15 amino acid flexible linker and the Vl region of the mouse 5T4 antibody. The flexible linker encodes 3 copies of the amino-acid sequence gly-gly-gly-gly-ser and the DNA sequence similarity between the repeats has been minimised to avoid the risk of recombination between the repeats when plasmids containing them are grown in *E. coli*.

The DNA sequences shown in Figure 1 can also be used to construct a variety of single-chain antibodies (Sabs) by coupling scFv-encoding sequences to a sequence encoding a Fc region to form an in-frame fusion. A Sab is constructed using a series of DNA cassettes which can be independently varied to suit particular purposes.

#### Cassette 1 – Translation initiation signal and signal peptide

In order to achieve correct translation initiation and secretion from mammalian cells, the following sequence is used:

```
aagcttCCACCATGG G ATGGAGCTGT ATCATCCTCTTCTTGGTAGC
AACAGCTACA GGTGTCCACT CC
```

This contains a convenient HindIII restriction site for cloning into expression vectors (lower case), the consensus translation initiation signal for mammalian cells (ANNATG<sup>Pu</sup>) and the coding sequence for a signal peptide sequence from an immunoglobulin gene.

#### Cassette 2 – scFv

The sequence of the secreted portion of the 5T4scFv.1 is shown in Figure 1. This molecule can be represented as Vh – (gly<sub>4</sub>-ser)<sub>3</sub> linker - VI.

5T4 scFv2 consists of the 5T4 variable region sequences connected in the order VI – flexible linker Vh. In this case the linker encodes the 20 amino-acid peptide (gly<sub>4</sub>-ser)<sub>4</sub>. A longer linker improves assembly of the scFv when the V-region segments are in this order. (Pluckthun et al in Antibody Engineering: a practical approach, ed McCafferty et al. 1996 OUP).

10

#### Cassette 3 – Heavy chain Constant region

The sequence of a human  $\gamma$ 1 constant region genomic clone is given in Ellison et al. 1982 Nucl. Acids res. 10: 4071-4079. This sequence contains constant-region introns in addition to the coding sequence. This is fused in-frame to the 3'-end of one of the scFv sequences from Cassette 2. Vectors for convenient assembly of such constructs are described (Walls et al. 1993 Nucl. Acids Res. 21:2921-2929).

A cDNA of a 5T4 Sab, designated 5T4Sab1 is shown in Figure 2, containing cassettes 1, 2 and 3.

20 The variable region of the 5T4 monoclonal antibody can also be humanised by a number of techniques, which are known in the art, including grafting of the CDR region sequences on to a human backbone. These can then be used to construct an intact humanised antibody or a humanised Sab (see Antibody Engineering: a practical approach, ed McCafferty et al. 1996 OUP).

25

For expression of a 5T4-specific scFv or Sab in human cells, the coding sequence is inserted into the vector pCIneo (Promega) under the control of a strong promoter and polyadenylation signal. The translation initiation signal and immunoglobulin leader (signal peptide)

sequence from Cassette 1 at the 5' end of the coding region ensure efficient secretion of the scFv or Sab from mammalian cells.

For expression of an intact Ig, two separate translation cassettes are constructed, one for the heavy chain and one for the light chain. These are separated by an internal ribosome - entry site (IRES) from the picornavirus FMDV (Ramesh et al. 1996 Nucl. Acids Res. 24: 2697-2700. Alternatively, each cDNA is expressed from a separate copy of the hCMV promoter (Ward and Bebbington 1995 In Monoclonal Antibodies ed Birch and Lennox. Wiley-Liss).

For production of retrovirus capable of expressing 5T4 antibody or immunoglobulin-like molecules with 5T4 specificity, the gene encoding a 5T4-based Sab, or a dicistronic message encoding heavy and light chains, is inserted into a retroviral vector in which retroviral genomic transcripts are produced from a strong promoter such as the hCMV-MIE promoter. A suitable plasmid is pHIT111 (Soneoka et al. 1995 Nucl. Acids Res. 23; 628-633) and the required gene is inserted in place of the LacZ gene using standard techniques. The resulting plasmid, pHIT-5T4.1 is then transfected into the FLYRD18 or FLYA13 packaging cell lines (Cosset et al. 1995 J. Virol. 69; 7430-7436) and transfectants selected for resistance to G418 at 1 mg/ml. G418-resistant packaging cells produce high titres of recombinant retrovirus capable of infecting human cells. The virus preparation is then used to infect human cancer cells and can be injected into tumours *in vivo*. The 5T4 Sab is then expressed and secreted from the tumour cells.

In pHIT111, the MoMLV LTR promoter-enhancer is used for expression of the therapeutic gene in the target cell. The vector can also be modified so that the therapeutic gene is transcribed from an internal promoter-enhancer such as one which is active predominantly in the tumour cells or one which contains a hypoxia regulated element. A

suitable promoter is a truncated HSV TK promoter with 3 copies of the mouse PGK HRE (Firth et al. 1994 Proc. Natl. Acad. Sci. 91: 6496-6500).

**Example 2 – Transfection of macrophages / monocytes with an expression vector encoding TBP.**

Peripheral blood mononuclear cells are isolated from human peripheral blood at laboratory scale by standard techniques procedures (Sandlie and Michaelsen 1996 In Antibody engineering: a practical approach. Ed McCafferty et al. Chapter 9) and at large scale by elutriation (eg Cephate from CellPro). Adherent cells (essentially monocytes) are enriched by adherence to plastic overnight and cells can be allowed to differentiate along the macrophage differentiation pathway by culturing adherent cells for 1-3 weeks.

Monocytes and macrophages are transfected with an expression vector capable of expressing TBP in human cells. For constitutive high level expression, the TBP is expressed in a vector which utilises the hCMV-MIE promoter-enhancer, pCI (Promega). For hypoxia-induced expression, the hCMV promoter is replaced by a promoter containing at least one HRE. A suitable promoter is a truncated HSV TK promoter with 3 copies of the mouse PGK HRE (Firth et al. 1994 Proc. Natl. Acad. Sci. 91: 6496-6500).

A variety of transfection methods can be used to introduce vectors into monocytes and macrophages, including particle-mediated DNA delivery (biolistics), electroporation, cationic agent-mediated transfection (eg using Superfect, Qiagen). Each of these methods is carried out according to the manufacturer's instructions, taking into account the parameters to be varied to achieve optimal results as specified by the individual manufacturer. Alternatively, viral vectors may be used such as defective Adenovirus vectors (Microbix Inc or Quantum Biotechnologies Inc).

### Example 3 – Assay for ADCC mediated by macrophages

Cells from primary human tumours or tumour cell lines which have been transduced with retrovirus expressing TBP are mixed with  
5 autologous or heterologous human macrophages, prepared as described in Example 2, for analysis of ADCC activity mediated by the TBP.

Alternatively, macrophages engineered to produce TBP as described in Example 2 can be used to direct ADCC on non-transduced tumour cells.

The assay is carried out according to standard procedures  
10 (Sandlie and Michaelsen 1996 In Antibody engineering: a practical approach. Ed McCafferty et al. Chapter 9) with appropriate modifications. Briefly, the effector cells (macrophages or freshly isolated monocytes) are suspended at  $3 \times 10^6$  cells / ml in the appropriate tissue culture medium (DMEM/Hepes, obtained from Life Technologies, containing 1% Foetal Calf  
15 Serum).  $3 \times 10^5$  tumour target cells, labelled with  $^{51}\text{Cr}$  are placed in each well of a round-bottomed microtitre plate in 0.1 ml culture medium. (Note the culture medium can include spent medium from the cells producing the TBP). 50  $\mu\text{l}$  effector cells are added to the wells, the plate is centrifuged at 300g for 2 min and incubated at  $37^\circ\text{C}$  for varying periods (eg 4 h) in a  
20 tissue culture incubator. The supernatant is then harvested by centrifugation and counted in a gamma counter. Results are expressed as percent lysis relative to total chromium release from an equivalent sample of target cells lysed with 0.1% Tween-20. The effector: target cell ratio can be varied in the assay to produce a titration curve.

25 For the prior stimulation of macrophage differentiation or priming, cytokines are added to the cultures.  $\text{IFN}\gamma$  (Sigma) is added at between 100 and 5000 U/ml. CSF-1 or GM-CSF (Santa Cruz Biotechnology) can also be added at appropriate concentrations.

**Example 4 – Analysis of efficacy in animal models**

Human tumour-derived cell lines and tissues are cultured *in vivo* in genetically immunodeficient, "nude" mice according to well established techniques (see for example Strobel et al. 1997 Cancer Res. 57: 1228-1232; McLeod et al. 1997 Pancreas 14: 237-248). Syngeneic mouse models, in which a syngeneic tumour line is introduced into an immunocompetent mouse strain may also be used. These serve as suitable animal models for evaluating gene delivery systems of the invention. Vectors or engineered cells are administered systemically or directly into the tumour and tumour growth is monitored in treated and untreated animals. This system is used to define the effective dose range of the treatments of the invention and the most appropriate route of administration.

Figure 1

1 GAGGTCCAGC TTCAGCAGTC TGGACCTGAC CTGGTGAAGC CTGGGGCTTC  
   E V Q L Q Q S G P D L V K P G A  
 51 AGTGAAGATA TCCTGCAAGG CTTCTGGTTA CTCATTCACT GGCTACTACA  
   S V K I S C K A S G Y S F T G Y Y  
 101 TGCACTGGGT GAAGCAGAGC CATGGAAAGA GCCTTGAGTG GATTGGACGT  
   M H W V K Q S H G K S L E W I G R  
 151 ATTAATCCTA ACAATGGTGT TACTCTCTAC AACCAGAAAT TCAAGGACAA  
   I N P N N G V T L Y N Q K F K D  
 201 GGCCATATTA ACTGTAGACA AGTCATCCAC CACAGCCTAC ATGGAGCTCC  
   K A I L T V D K S S T T A Y M E L  
 251 GCAGCCTGAC ATCTGAGGAC TCTGCGGTCT ATTACTGTGC AAGATCTACT  
   R S L T S E D S A V Y Y C A R S T  
 301 ATGATTACGA ACTATGTTAT GGACTACTGG GGTCAAGTAA CCTCAGTCAC  
   M I T N Y V M D Y W G Q V T S V  
 351 CGTCTCCTCA GGTGGTGGTG GGAGCGGTGG TGGCGGCACT GGCGGCGGCG  
   T V S S G G G G S G G G G T G G G  
 401 GATCTAGTAT TGTGATGACC CAGACTCCCA CATTCTGCT TGTTCAGCA  
   G S S I V M T Q T P T F L L V S A  
 451 GGAGACAGGG TTACCATAAC CTGCAAGGCC AGTCAGAGTG TGAGTAATGA  
   G D R V T I T C K A S Q S V S N  
 501 TGTAGCTTGG TACCAACAGA AGCCAGGGCA GTCTCCTACA CTGCTCATAT  
   D V A W Y Q Q K P G Q S P T L L I  
 551 CCTATACATC CAGTCGCTAC GCTGGAGTCC CTGATCGCTT CATTGGCAGT  
   S Y T S S R Y A G V P D R F I G S  
 601 GGATATGGGA CGGATTTTAC TTTACCATC AGCACTTTGC AGGCTGAAGA  
   G Y G T D F T F T I S T L Q A E  
 651 CCTGGCAGTT TATTTCTGTC AGCAAGATTA TAATTCTCCT CCGACGTTTCG  
   D L A V Y F C Q Q D Y N S P P T F  
 701 GTGGAGGCAC CAAGCTGGAA ATCAAACGG  
   G G G T K L E I K R

Figure 2

1 AAGCTTCCAC CATGGGATGG AGCTGTATCA TCCTCTTCTT GGTAGCAACA  
A S T M G W S C I I L F L V A T

51 GCTACAGGTG TCCACTCCGA GGTCCAGCTT CAGCAGTCTG GACCTGACCT  
A T G V H S E V Q L Q Q S G P D

101 GGTGAAGCCT GGGGCTTCAG TGAAGATATC CTGCAAGGCT TCTGGTTACT  
L V K P G A S V K I S C K A S G Y

151 CATTCACTGG CTACTACATG CACTGGGTGA AGCAGAGCCA TGGAAAGAGC  
S F T G Y Y M H W V K Q S H G K S

201 CTTGAGTGGA TTGGACGTAT TAATCCTAAC AATGGTGTTA CTCTCTACAA  
L E W I G R I N P N N G V T L Y

251 CCAGAAATTC AAGGACAAGG CCATATTAAC TGTAGACAAG TCATCCACCA  
N Q K F K D K A I L T V D K S S T

301 CAGCCTACAT GGAGCTCCGC AGCCTGACAT CTGAGGACTC TGCGGTCTAT  
T A Y M E L R S L T S E D S A V Y

351 TACTGTGCAA GATCTACTAT GATTACGAAC TATGTTATGG ACTACTGGGG  
Y C A R S T M I T N Y V M D Y W

401 TCAAGTAACC TCAGTCACCG TCTCCTCAGG TGGTGGTGGG AGCGGTGGTG  
G Q V T S V T V S S G G G G S G G

451 GCGGCACTGG CGGCGGCGGA TCTAGTATTG TGATGACCCA GACTCCCACA  
G G T G G G G S S I V M T Q T P T

501 TTCCTGCTTG TTTCAGCAGG AGACAGGGTT ACCATAACCT GCAAGGCCAG  
F L L V S A G D R V T I T C K A

551 TCAGAGTGTG AGTAATGATG TAGCTTGGTA CCAACAGAAG CCAGGGCAGT  
S Q S V S N D V A W Y Q Q K P G Q

601 CTCCTACACT GCTCATATCC TATACATCCA GTCGCTACGC TGGAGTCCCT  
S P T L L I S Y T S S R Y A G V P

651 GATCGCTTCA TTGGCAGTGG ATATGGGACG GATTTCACCT TCACCATCAG  
D R F I G S G Y G T D F T F T I

701 CACTTTGCAG GCTGAAGACC TGGCAGTTTA TTTCTGTCAG CAAGATTATA  
S T L Q A E D L A V Y F C Q Q D Y

751 ATTCTCCTCC GACGTTCCGT GGAGGCACCA AGCTGGAAAT CAAACGGGCC  
N S P P T F G G G T K L E I K R A

801 TCCACCAAGG GCCCATCGGT CTTCCCCCTG GCACCCTCCT CCAAGAGCAC  
S T K G P S V F P L A P S S K S

851 CTCTGGGGGC ACAGCGGCCC TGGGCTGCCT GGTCAAGGAC TACTTCCCCG  
T S G G T A A L G C L V K D Y F P

901 AACCGGTGAC GGTGTCGTGG AACTCAGGCG CCCTGACCAG CGGCGTGCAC  
E P V T V S W N S G A L T S G V H

951 ACCTTCCCGG CTGTCCTACA GTCCTCAGGA CTCTACTCCC TCAGCAGCGT  
       T F P A V L Q S S G L Y S L S S  
 1001 GGTGACCGTG CCCTCCAGCA GCTTGGGCAC CCAGACCTAC ATCTGCAACG  
       V V T V P S S S L G T Q T Y I C N  
 1051 TGAATCACAA GCCCAGCAAC ACCAAGGTGG ACAAGAAAGT TGAGCCCAAA  
       V N H K P S N T K V D K K V E P K  
 1101 TCTTGTGACA AAACCTCACAC ATGCCACCG TGCCACGAC CTGAACTCCT  
       S C D K T H T C P P C P A P E L  
 1151 GGGGGGACCG TCAGTCTTCC TCTTCCCCC AAAACCCAAG GACACCCTCA  
       L G G P S V F L F P P K P K D T L  
 1201 TGATCTCCCG GACCCCTGAG GTCACATGCG TGGTGGTGGG CGTGAGCCAC  
       M I S R T P E V T C V V V D V S H  
 1251 GAAGACCCTG AGGTCAAGTT CAACTGGTAC GTGGACGGCG TGGAGGTGCA  
       E D P E V K F N W Y V D G V E V  
 1301 TAATGCCAAG ACAAAGCCGC GGGAGGAGCA GTACAACAGC ACGTACCGTG  
       H N A K T K P R E E Q Y N S T Y R  
 1351 TGGTCAGCGT CCTCACCGTC CTGCACCAGG ACTGGCTGAA TGGCAAGGAG  
       V V S V L T V L H Q D W L N G K E  
 1401 TACAAGTGCA AGGTCTCCAA CAAAGCCCTC CCAGCCCCCA TCGAGAAAAC  
       Y K C K V S N K A L P A P I E K  
 1451 CATCTCCAAA GCCAAAGGGC AGCCCCGAGA ACCACAGGTG TACACCCTGC  
       T I S K A K G Q P R E P Q V Y T L  
 1501 CCCCATCCCG GGATGAGCTG ACCAAGAACC AGGTCAGCCT GACCTGCCTG  
       P P S R D E L T K N Q V S L T C L  
 1551 GTCAAAGGCT TCTATCCCAG CGACATCGCC GTGGAGTGGG AGAGCAATGG  
       V K G F Y P S D I A V E W E S N  
 1601 GCAGCCGGAG AACAACTACA AGACCACGCC TCCCGTGCTG GACTCCGACG  
       G Q P E N N Y K T T P P V L D S D  
 1651 GCTCCTTCTT CCTCTACAGC AAGCTCACCG TGGACAAGAG CAGGTGGCAG  
       G S F F L Y S K L T V D K S R W Q  
 1701 CAGGGGAACG TCTTCTCATG CTCCGTGATG CATGAGGCTC TGCACAACCA  
       Q G N V F S C S V M H E A L H N  
 1751 CTACACGCAG AAGAGCCTCT CCCTGTCTCC GGGTAAATGA GTGCGACGGC  
       H Y T Q K S L S L S P G K - V R R  
 1801 CAAGCTT  
       P S

PCT GB 98/01627

Filed 4/6/98

D. Young & Co.